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**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5)

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INTERNATIONAL APPLICATION NO.
PCT/US99/29508

INTERNATIONAL FILING DATE
14 December 1999

PRIORITY DATE CLAIMED

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TITLE OF INVENTION
APPARATUS AND METHODS FOR COMBINATORIAL CHEMICAL ANALYSIS

APPLICANT(S) FOR DO/EO/US
Louis D'Esposito

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 15. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ A FIRST preliminary amendment.
- ☐ A SECOND or SUBSEQUENT preliminary amendment.
13. ☐ A substitute specification.
14. ☐ A change of power of attorney and/or address letter.
15. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.50) <div style="font-size: 1.5em; font-weight: bold; margin-top: 10px;">09/ 857953</div>		INTERNATIONAL APPLICATION NO. PCT/US99/29508		ATTORNEY'S DOCKET NUMBER 17932	
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17. <input checked="" type="checkbox"/> The following fees are submitted: <div style="margin-left: 20px;"> Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO \$ 860.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) \$ 690.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$ 710.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445 (a)(2)) paid to USPTO \$ 1,000.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) \$ 100.00 </div>				CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 860.00	
Surcharge of \$ 130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$ 130.00	
Claims	Number Filed	Number Extra	Rate		
Total Claim	12 - 20 =	0	X \$ 18.00	\$ 0.00	
Independent Claims	2 - 3 =	0	X \$ 80.00	\$ 0.00	
Multiple dependent claim(s) (if applicable)			\$ 0.00	\$ 0.00	
Processing fee of \$ 0 for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$ 0.00	
TOTAL NATIONAL FEE =				\$ 990.00	
				Amount to be refunded:	\$
				charged:	\$

a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 04-1512 in the amount of \$ 990.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-1512 . A duplicate copy of this sheet is enclosed.	<p>Note: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</p> <div style="border: 1px solid black; padding: 10px; margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 35%;"> SEND ALL CORRESPONDENCE TO: Graham E. Taylor The Dow Chemical Company Intellectual Property P.O. Box 1967 Midland, Michigan 48641-1967 UNITED STATES OF AMERICA </div> <div style="width: 60%;"> Signature: <u><i>Burke M. Halldorson</i></u> Burke M. Halldorson , Registration No. 24,642 Date: <u>12 June 2001</u> </div> </div> </div>
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APPARATUS AND METHODS FOR COMBINATORIAL
CHEMICAL ANALYSIS

Field of the Invention

This invention pertains to apparatus and methods for chemical analysis of an array of zones, e.g., reaction sites, for the presence of a material sought to be identified. The invention finds particular utility in the field of combinatorial chemistry and in applications where high throughput screening is sought.

Background of the Invention

Combinatorial chemistry is a research technique that has found particular applicability in preparing and/or screening diverse materials, especially in large numbers for determining potential properties and utilities such as catalytic activity. Often, the amounts of material needed for the screening can be relatively small, and not only can arrays of materials for analysis be relatively compact but also numerous materials can be evaluated at the same time. Rapid screening methods are thus advantageous for evaluating arrays of the materials for specific properties.

The analytical techniques for combinatorial chemistry have either been cursory or very complex. For instance, thermal sensors, e.g., infrared thermal imagers, have been proposed to determine the heat production from regions (or sites) in the arrays. See, for instance, A. Holzwarth, et al., Angew. Chem. Intl. Ed., 1998, 37, No. 19, 2644 to 2647; M.T. Reetz, et al., Angew. Chem. Intl. Ed., 1998, 37, No. 19, 2644 to 2647 and WO1998EP0008214. Although thermal imaging has been used successfully for the specific systems of interest, this approach has its limitations and shortfalls. Thermal imaging as a screening tool relies on the principle that chemical

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reactions have associated with them a heat, namely, the heat of reaction which may be either endothermic heat or exothermic heat. Hence, if an array of spatially resolved catalyst compositions were exposed to reagents and reaction conditions suitable for producing a desired product, the sites having catalyst compositions which produced a chemical reaction would be detected by the thermal imaging device. Thermal imaging devices can be very sensitive (ca. 0.01 degree Kelvin). Even weak activity as indicated by a temperature either above or below the background temperature can be detected. Thermal imaging devices as analysis tools, even for high throughput screening as frequently used in combinatorial chemistry, may be of limited value. The temperature differential only indicates that a reaction is occurring, not that the sought reaction is taking place. Thus the potential for false "hits" may hinder and not aid in catalyst lead generation.

Other techniques proposed for high throughput screening of arrays of diverse materials are high performance liquid chromatography and gas chromatography both which typically require handling or sampling the material in each site. These techniques require the ability to regiospecifically remove liquid in a site or gas evolved from a site in the array. For instance, International Patent Application WO 98/15969 discloses selectively withdrawing gas evolved from each site and then analyzing it by, for instance, mass spectroscopy. While these techniques identify whether the sought product is being produced, the apparatus for the regiospecific sampling may be complex and expensive, especially where the sites on the array are small. These techniques also require that one site be sampled at a time. For the large libraries desired to be used for combinatorial chemistry, the time for analysis can be quite extensive and thus undercut the ability to achieve high productivity benefits.

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International Patent Application WO 98/15813, herein incorporated by reference, discloses the characterization of libraries of diverse materials using infrared imaging and infrared spectroscopy techniques. The application states at page 5, lines 28 et seq.:

According to another aspect of the invention, identification and characterization of the condensed solid or liquid phase products is achieved, wherein library elements are characterized by their specific infrared absorption or reflectance. Such materials may be the product of reactions, for example, in the gas phase polymerization of ethylene to condensed phase polyethylene or in the hydrolysis of liquid dimethyldichlorosilane to elastomeric polydimethylsiloxane. In one embodiment specific molecular vibrations are evaluated by measuring the IR absorption.

Typically, the radiation from a monochromatic infrared source is passed through the library and the intensity of the transmitted beam is measured as a function of time during the progression of a reaction. In an alternate embodiment, the library is irradiated with polychromatic infrared radiation and an infrared bandpass filter is used to confine the detection to specific wavelength regions of the infrared spectrum.

This PCT application thus describes using an infrared transparent substrate for the library of materials in order to permit the infrared radiation to pass to a detector on the opposite side of the substrate from the radiation source. The need to have a transparent substrate limits the range of evaluations that can be conducted and the equipment that can be used. This PCT application also discloses FTIR imaging that is not real time imaging. Interferograms (spatially resolved) are collected onto an array detector and mathematically transformed to spectra. These spectra can be post processed to display an image of the field of view which contains only selected absorption

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frequencies. This post processing does not allow for real time observation of activity. Currently most state of the art of commercial focal plane array detectors have an image field of only a fraction of a centimeter. Thus this equipment would have reduced attractiveness for parallel assessment of large reaction zone arrays. Further, resolution of locations of activity can be difficult if mixing of reaction products can occur.

A desire exists to extend the use of combinational chemistry techniques to a multitude of applications including the development of new materials, determining the reactivity or catalytic activity of materials and to develop enhanced chemical and biotechnological processes.

Summary of the Invention

In accordance with this invention, the presence of a sought material is determined through irradiation of zones in an array with electromagnetic radiation of a predetermined wavelength which is absorbed by the sought material and detecting by backscattered radiation whether such radiation is absorbed as an indication of the presence of the sought material. The processes and apparatus of the invention are particularly useful where the material sought to be detected has a unique, or a unique combination, of absorbency properties as compared to other materials present or potentially present in the zone. Since detection is by backscatter, substantial flexibility is provided in the design of the zones in the array. In preferred aspects of the invention, the zones may comprise means to supply differing fluid materials to different zones of the same array.

In the broad aspects, the apparatus of this invention comprise an array of a plurality of zones capable of containing diverse material; an electromagnetic radiation source capable of generating

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radiation of a predetermined wavelength and adapted to irradiate one or more zones, and a detector which is adapted to detect reflectance from one or more zones being irradiated of radiation of said radiation.

In the broad aspects, the processes of this invention for detecting the presence of a component comprise irradiating one or more of a plurality of zone containing material with an electromagnetic radiation having a predetermined wavelength capable of being absorbed by the component and detecting by backscatter, the absorption of the electromagnetic radiation in one or more of the plurality of zones containing material to determine the likely presence of said component.

Brief Description of the Drawings

In the drawings:

Figure 1 is a schematic representation of an apparatus of this invention;

Figure 2 is a schematic representation of a portion of an apparatus in accordance with this invention which illustrates oriented receptors that facilitate operation of the processes of the invention;

Figure 3 is a schematic representation of an apparatus in accordance with this invention wherein the device for detecting radiation is movable for selective positioning with respect to each zone of the array

Figure 4 is a cross-sectional depiction of a reactor assembly useful in the apparatus of this invention; and

Figure 5 is a schematic representation of of an apparatus in accordance with this invention wherein the device for detecting radiation is movable using a robotic positioning arm.

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Detailed Description

The processes and apparatus of this invention are particularly useful in detecting the presence of components, especially single chemical components, that possess an ability to selectively absorb one or more electromagnetic radiation wavelengths. The components may be solid, liquid or gaseous.

Many chemicals have absorption spectra, i.e., they absorb, to a greater or lesser extent, a plurality of disparate electromagnetic radiation wavelengths. This is the principle upon which absorption spectroscopies such as infrared spectroscopy is based. Preferably, the predetermined wavelength is one which is strongly absorbed by the sought component for detection and that wavelength is different than the wavelengths that are absorbed by other materials in the irradiated zone and different than the wavelengths that are absorbed by potential components in the zone. For instance, if the purpose of the detection is to ascertain the generation of a reaction product, the absorbed wavelength should not be shared with potential undesired reaction products or starting reagents.

Backscatter radiation detection provides many advantages over transmission-type spectroscopy. For example, transmission spectroscopy requires special zone design to allow the radiation to pass through the zone. This limits the types of zones that can be used. Further, alignment of the radiation source and the detector is required, which increases in complexity to inspect each zone in the apparatus. In advantageous aspects of this invention, the backscatter occurs at the location of the component sought to be detected. This enables, for instance, an image to be achieved to readily isolate those zones in which the sought component is present. Moreover, considerable flexibility is provided in zone configuration,

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which is particularly attractive where the zones comprise reactors and thus can contain, e.g. catalyst, liquid solvents and the like.

In backscatter radiation detection, the presence of a sought material is determined through irradiation of zones in an array with electromagnetic radiation having a predetermined wavelength which is selectively absorbed by the sought material. The amplitude of the radiation of the predetermined wavelength will become attenuated as it passes through a fluid containing the sought material and becomes absorbed. Any of the radiation not being absorbed as the radiation penetrates the fluid sample being analyzed for the presence of the sought material may be reflected. As it returns through the fluid, it can become further attenuated by absorption by the sought material. The attenuation of the radiation determined from the backscatter thus not only can qualitatively indicate the presence of the sought material, but also the degree of attenuation can be used to quantitatively determine the amount, or concentration, of the sought component that is present.

In an aspect of this invention, means are provided to reflect the electromagnetic radiation. This reflectance results in enhanced contrast and thus a higher signal to noise ratio for determining the presence of the sought component. The reflectance may be enhanced by any suitable surface capable of reflecting the radiation such as mirrors and polished metal surfaces in the apparatus. Especially where the sought component may be in a low concentration in the fluid, the depth of the fluid which is subjected to the radiation may be increased. For instance, the effluent from a reactor in the array may be directed through a pipe such that axially-directed radiation passes through a sufficient length of the fluid to achieve a level of absorption to facilitate detection. A reflector at the end of the pipe to reflect the radiation back through the pipe for

further attenuation enhances the benefit provided by the pipe. The length of pipe required for a particular analysis can be readily determined by one skilled in the art based upon the above principles, and the length is often between about 1 to 100 centimeters.

The electromagnetic radiation wavelength may be selected over a wide range of wavelengths, e.g., within the range of about 10^{-14} to 10^4 meters. Often the wavelength is in the mid-infrared wavelength range, e.g., within the range of about 2 to 25 microns.

The source of the radiation may generate a monochromatic or polychromatic radiation. If the source of the radiation is polychromatic then the backscatter determination should be selective to the sought wavelength, e.g., by the use of a narrow bandpass filter. The source of monochromatic radiation may be any convenient source that provides sufficient energy of radiation for detection. For instance, radiation of more than one wavelength can be generated and then filtered or diffracted into a spectrum to provide the monochromatic radiation source. Most preferably the source of the radiation is a laser that generates the sought radiation wavelength. Gas and solid state lasers that can be tuned to desired frequencies are available and thus extend the usefulness of the apparatus of the invention for determination of the presence of more than one material, or to seek more than one absorption frequency for identification.

Where a monochromatic radiation source is used, the detector need only be able to ascertain whether or not the radiation impinging in the zone of the array is being absorbed. The backscatter of the radiation can be detected by any suitable means known to those skilled in the art. One particularly useful technique is using a video camera that focuses on the zone. The signals from the video camera can be depicted on a monitor for visualization of the region of radiation absorption. The relative amplitude of the backscatter radiation may, if

desired, be used to obtain additional analytical benefits. First, the amount of absorption of the radiation may assist in ascertaining the amount of the material present, and second, a determination may be made between two or more components, each capable of absorbing radiation of the predetermined wavelength but to different degrees. For instance, with respect to the latter, chemical compounds may differ in their ability to absorb radiation of a given wavelength. In one, the radiation may be strongly absorbed and in another moderately or weakly absorbed.

As can be readily appreciated, the band width of a monochromatic radiation can comprise more than one frequency. However, it is desired that the band width be sufficiently narrow that only the absorption of interest can be detected. Often the band width is within 5, preferably within 1, percent (based on wavelength) of the sought frequency.

With respect to polychromatic radiation, the detector needs to be sensitive to the sought reflected radiation. Several techniques include diffracting the reflected radiation from the zone and determining the absorption spectra, particularly of the wavelength or wavelengths of interest. This method has the advantage of being able to determine the presence of more than one absorption band to help in identification of the material being irradiated. Other techniques include the use of filters or detectors that are sensitive, e.g., fluoresce, with radiation of the given wavelength.

In accordance with the invention, an array of zones are present and contain diverse material as permit, if desired, high productivity chemical analyses. One or more of the zones can be irradiated at a given time and one or more of these zones being irradiated can be observed for radiation backscatter of a given wavelength. In one embodiment more than one zone is irradiated and

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all irradiated zones are observed. In another embodiment, more than one zone is irradiated and only one zone is observed at a time. In yet another embodiment more than one zone is observed and one zone is irradiated at a time. In another embodiment, one zone is irradiated at a time and only that zone is observed. The choice of the embodiment will depend upon the available equipment, the number of zones in the array and the purpose of the analysis. By way of example, if the purpose is to screen a plurality of catalytic sites, with a site being a zone, simultaneous irradiation of all or a significant portion of the array encompassing a plurality of zones, with simultaneous observation may be adequate. If the zones are micro reactors requiring reactor structure such as walls, fluid feed and egress piping, and catalyst, the spatial pattern of the reactors in the array may be so great that simultaneous, multiple irradiation and observation is impractical.

A particularly convenient mode of operation is to irradiate one zone, and perhaps even a portion of a zone, at a time and focus detection of absorbance of the radiation at that zone. The advantages are that for a given energy of the radiation source the radiation can be more concentrated making easier detection and automated data collection is facilitated. In a further preferred embodiment, the radiation source is a laser and the foot print (beam diameter) of the laser in the zone has a major dimension of less than about 5 millimeters, preferably less than about 2 millimeters, and sometimes less than about 0.5 millimeter, in order to selectively determine if, and then where, the sought component is in the zone. This technique is particularly attractive where numerous materials are in close proximity. A particularly attractive use of a laser is to raster a fine beam from the laser over the area being scanned. With rapid rastering, e.g., substantially covering the area to be observed in less

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than one second, and preferably less than 0.1 second, real time observations can be obtained. The reflected electromagnetic radiation can be detected by a synchronized video camera and displayed on a monitor. Such a system for imaging materials, especially gases, is described in US 4,555,627, herein incorporated by reference. Imaging products based on this technology have been developed and marketed by Laser Imaging Systems Inc., Punta Gorda, Florida, United States of America. Advantageously, where the sought component is to be contained in an off-gas from a reaction zone, a highly reflective background such as a polished gold film is used to provide contrast and enhance the ability to detect the sought component.

When zones in the array are reactors, it may be desirable to focus the irradiation or observation in only a region. For instance, if the sought material for detection is a gas, the region of focus may be on the gas outlet for the reactor. On the other hand, the desire is to identify the generation of an intermediate or a solid or liquid product, the region of focus may be on the catalyst or catalyst-containing solution. Focusing and magnification techniques may find particular utility in this regard.

The array combines a plurality of zones, e.g., at least 2 and preferably at least 3 or 6 or more zones. The maximum number of zones will depend upon the economics of the apparatus. Minimization of the zones will permit more zones to be included. The literature has reported arrays of greater than 100 zones, and WO 98/15813 contemplates over 10 million regions being present per square centimeter in arrays used for combinatorial chemistry. This patent describes several techniques for the preparation of arrays on a fixed substrate for use in combinatorial chemistry analyses. Nevertheless, the specific design of the array will be influenced by the type of treatment each site will be undergoing. For instance, homogeneous

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catalytic reactions may be conducted in an apparatus such as shown in the drawings where a gas can be bubbled through a solution containing the catalyst. An advantage of the processes of the invention is that it is not critical to have a high density of regions in an array in order to obtain high productivity analyses.

The design of the zone can be varied depending upon the sought analysis. At our extreme, the zone may only be a site where a sample to be irradiated is fixed. At the other extreme, the zone may be a complex reactor containing catalyst, one or more input lines and one or more output lines, and a heat or cooling source. In fact, the zone may contain unit operations other than a reactor or even include more than one reaction zone.

As can be seen from this disclosure, the material sought may be solid, liquid or gas. The analysis may be on preexisting materials or may be on materials sought to be generated in the zones, i.e., reaction products. Exemplary of reaction products are solids, especially crystalline solids, liquids or dissolved materials in a solvent of the reaction, or gases, the reactions may be batch, i.e., all materials required for the reaction are placed in the zone prior to commencement of the analysis, or may be continuous or semicontinuous such as by passing a gas over a solid catalyst.

In one preferred aspect of this invention is a combination of a video imaging system and a reaction vessel used for detecting the activity of a catalyst composition for suitability to produce a target molecule by providing a visual display of the vapor cloud of the product vapor in the proximity to the catalyst composition producing said product composition. When used as a screening tool to assess the catalytic activity of a library of catalyst compositions as may be assembled using combinatorial chemical principles, this technique provides for the simultaneous, rapid assessment of catalyst activity of

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each of the library elements. In this fashion, high volumes of catalyst compositions can be screened for catalytic activity under actual operating conditions by suitable interfacing of the video imaging system and the reaction autoclave.

The video imaging device for detecting the presence of vapor products from the vicinity of a catalyst composition is based on the principle of backscatter absorption gas imaging or BAGI for short. In the BAGI system visual displays are produced by radiation augmentation of the field of view of an imaging device by radiation corresponding to an absorption line of the component to be detected. The field of view of the imager is irradiated by a laser. The imager receives both backscattered laser light and background radiation. When the detectable gas, liquid or solid is present, the backscattered laser light is highly attenuated, producing a region of contrast or shadow on the image. A flying spot imaging system is utilized to synchronously irradiate and scan the area to laser power requirements. The image signal is processed to produce a video display. Using this device provides a real time image only of materials which absorb at the excitation wavelength of the laser. Consequently, specific activity can be discerned by real time reference to the real time video image. Also, infrared laser tunability allows selection of incident radiation wavelengths and thus flexibility to selectively image, in real time, a wide diversity of infrared absorbing materials.

It should be readily appreciated that the electromagnetic radiation absorption analysis of this invention can be combined with other techniques. For instance, thermal imaging of a site in combination with the use of this invention will reveal not only the generation of the sought material but also an indication of the rate of its formation due to changes in temperature. More complex techniques

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such as mass spectroscopy can be focused on only those sites which, by the use of this invention, reveal the presence of the sought material.

One aspect of this invention is further described in connection with the drawing. The drawing, however, is not in limitation of the invention.

One embodiment of this invention can be ascertained by reference to Figure 1. In this figure the screening device consists a reaction vessel 1 into which a plurality of diverse, spatially resolved catalyst compositions are placed inside reactor tubes 2. The catalyst may be solid, in which case the reaction is heterogeneous, or may be contained in a solution for homogeneous reactions. The reaction vessel is capable of traversing a range of temperatures and reaction pressures as is typical for evaluating catalysts. A window 3 is fabricated into the reaction vessel and is composed of a material which is transparent to the laser radiation of the BAGI device. This material, for example, could be composed of potassium bromide, sodium chloride, sapphire, diamond, calcium fluoride, silicon, or any of a number of IR transmitting window materials known in the art. The window is fastened to the reaction vessel by suitable flanges. Placed in contact with this window is the BAGI camera 4, whose field of view contains the plurality of catalyst compositions. Reagent enters through connector lines (5A, 5B or 5C) and passes up from section (A) of the reaction vessel through the plurality of catalyst beds 2, and through to section (B) of the reaction vessel and finally to vent line 6. Section A and section B are separated by plate C which is highly reflective as a result of either polishing the surface or coating the surface with a highly reflective metal such as gold. Other highly reflective coatings or films may be used as well. While the coating is not essential to the broad aspects of the invention, a benefit is enhanced reflection of the radiation to facilitate detection. As the reagent moves up through the

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catalyst beds, catalytic activity commences in those tubes which contain active catalysts. The BAGI device displays on a monitor and records on video tape, images of the plumes emanating from the tubes. Positive plume images emanating from specific tubes indicate that these specific tubes contain catalysts which have activity toward the sought after product.

As shown in the drawing, lines 5A and 5B are adapted to feed different reactants to separate reactors 2. Line 5C introduces yet a different reactant into the lower plenum of vessel 1 to commonly feed two additional reactors 2. In a preferred embodiment, the ambient temperatures within the vessel 1 are maintained relatively uniform (except at the regions where a reaction may be occurring) to minimize thermal artifacts in interpreting the reflectance observations. The fluids in sections A and B may be useful in maintaining a desired uniform ambient temperature. While as depicted, the apparatus is particularly adapted for heterogeneous or homogeneous catalyst screening wherein a gas is passed over the catalyst or through the solution containing the catalyst, it should be evident that the fluid passing through reactor 2 may be a liquid and instead of a plume, the liquid spills over the top of the reactor.

In another embodiment of this invention the reaction vessel is equipped with two IR transmitting windows. Connected to one window is a BAGI video imager and to the other 7 a conventional IR thermal imaging camera 8. The purpose of the thermal imaging camera is that once the BAGI camera detects which catalyst beds are the active ones for the product of interest, the IR thermal imaging camera can simultaneously detect which of these positive "hits" has associated with it the greatest temperature differential from background. In this manner, a relative assessment of catalyst activity among the active catalysts can be derived.

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In yet another embodiment of this invention, the reaction vessel is designed to contain a plurality of BAGI imagers, represented as 4 and 8 in the drawing, each coupled to the reaction vessel via an IR transmitting window, represented as 3 and 7 in the drawing. Each BAGI uses a scanning laser of different wavelength and camera which are selected so as to detect other specific products that may result from catalytic activity such as by-products or unwanted products. In this way one can not only rapidly screen for active catalysts, but also assess the degree to which each positive catalyst also promotes side or unwanted reactions. This feature is valuable for selecting only the most promising catalyst leads for more intensive study.

Note that this device is not limited by any design of the reaction vessel nor by the spatial relationship of the BAGI camera to the reaction vessel as depicted in Figure 1. Several alternative reactor designs and camera placements could be used in carrying out the objective of rapidly screening catalyst libraries for catalytic activity as described herein.

It is possible to use the apparatus of this invention with other analytical apparatus. For example, the effluent from line 6 may be analyzed by another analytical technique for the presence of the sought material, e.g., by gas chromatography, infrared spectroscopy, nuclear magnetic resonance, etc. Upon determining the presence of the sought, the radiation and detection system may be activated to determine the reactor or reactors in which the sought material is being produced.

In Figure 2, only a portion of an apparatus such as being of the general type disclosed in Figure 1 is shown. In the description, like identification numbers reference similar items to those in Figure 1. Reactor tubes 2 are depicted as being located in plate C. Lines 5 provide reactant to each of the reactors 2. The apparatus has radiation

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detector 4 positioned in a fixed location. Each reactor 2 is provided with an oriented receptor for the fluid passing from reactor 2. The oriented receptor 20 is shown as a tube through the bore of which the fluid passes to enter zone B of the apparatus. The orientation is such that the detector 4 views the tube axially. Hence, the reactor positioned immediately below detector 4 has a tube having a common axis 22 with axis 24 of the reactor. Those reactors offset from the detector have tubes of increasing angle with the axis of the reactor such that the detector views the bore of the tube. In this aspect of the apparatus of the invention, a long path is defined to increase the number of molecules of sought material along the path of the electromagnetic radiation and thereby facilitate detection of a sought component that may be in a low concentration in the reactor effluent.

Figure 3 is also a schematic representation of an apparatus similar to those described in Figures 1 and 2. Again, like identification numbers indicate like parts. In this embodiment, detector 30 is movably mounted such that it can be positioned directly above each reactor 2. Detector 4 has radiation source 8 attached thereto to enhance the focus of the radiation in the tube being irradiated. As shown, detector 4 is mounted on wheeled carriage 30, the wheels of which ride on track 38. Positioning motor 32 controls the length of cable 35 which is fixed to detector 4. Diametrically opposed to positioning motor 32 is spring coil spool 34 which through cable 36 assures that cable 35 is maintained taut. Hence, the positioning motor can move the detector to predetermined locations along track 38. The positioning motor can conveniently be computer controlled.

Figure 5 is a schematic representation similar to that shown in Figure 3. Like parts are identified by like numbers. In this embodiment, the detector and light source are suspended above window 3 by robotic arm 50 which is able to move the detector and

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light source from one position to another position over a selected reactor 2. The receptors 20 for each of the reactors are thus vertical. The robotic arm 50 is moved by positioning motor 54 which is controlled by computer 52. Computer controlled robotic arms are well known to those skilled in the art, especially for robotic assembly procedures and are capable of accurate positioning of the detector.

Figure 4 is a depiction of reactor 400 that can find application in the apparatus of this invention. The reactor comprises cylindrical body 402 which at the top is threaded on the inside and outside. The outside threads enable it to be positioned in separator plate C such as shown in Figures 1, 2, 3 and 5. The inside threads receive top plate 404. This top plate has a radially extended lip with two concentric grooves on its lower face which receive o-rings 408 and 410. O-ring 408 is positioned such that it contacts the end edge of cylinder 402 to assure a fluid-tight seal, and o-ring 410 is positioned to contact the top surface of separator plate C to assure a fluid-tight seal. Top plate 404 has a central bore which receives at the top receptor 406. At the lower face of top plate 404 is attached support bar 414 which straddles the bore. Support bar 414 is narrow in width such that only a limited obstruction is provided to the flow of fluid into the bore and receptor 406. Support bar is attached to the top plate by screws 416. Positioned on support bar 414 at the vertical center line of the receptor 406 is horizontally positioned circular mirror 412. The face of circular mirror 412 is highly reflective and may be polished metal, preferably gold. The tubes themselves may have their interiors polished to enhance reflectance. Radiation passing downwardly through receptor 406 is thus reflected back by the circular mirror. The lower end of the cylindrical body 402 is closed with bottom plate 418. Bottom plate 418 has a radially extended lip which has a concentric groove adapted to receive o-ring 428 to provide a fluid-tight seal with the end of the

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cylindrical body. The upper face of bottom plate 418 has resting on it screen 420 which prevents solid contents of the reactor such as catalyst from falling out of the reactor through a central bore in the bottom plate. The central bore of bottom plate 418 receives nipple 422 to which feed supply line 424 is attached with the aid of clamp 426. Other means for connecting the feed supply line to the nipple could be used as are known in the art.

One additional benefit of this invention is the ability to record on a VCR device BAGI activity inside the reaction vessel for a continuous amount of time. By doing so, catalyst library elements which may not become active immediately upon interacting with reagent, but which may require an induction period to develop activity, will also be detected and therefore not overlooked for consideration as potential catalysts. Also, it is possible to ascertain information about catalyst aging via review of the video images as time progresses.

Any of a number of image analysis tools as are known in the art can be used to enhance any of the images so recorded and to quantify (if only semi-quantitatively) via grey scale comparisons, the relative production rate among the active catalyst compositions in the tested library.

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CLAIMS

- 5 1. An apparatus used in combinatorial chemistry comprising:
- 10 a. an array of zones each consisting of or comprising a reactor and being capable of containing diverse material, each said zone also being capable of containing a reaction product of the reactor;
- 15 b. an electromagnetic radiation source capable of generating radiation of a predetermined wavelength which can be absorbed by a sought material in the reaction product of the reactor;
- 20 c. a detector which is adapted to detect said electromagnetic radiation; and
- 25 d. a reflective surface in said zone adapted to receive said electromagnetic radiation after passing through said reaction product in the zone and reflect said radiation through said reaction product to said detector.
- 30 2. The apparatus of claim 1 in which the radiation source is a laser.
3. The apparatus of claim 2 in which the radiation source is infrared radiation.
4. The apparatus of claim 3 in which the reactors have means to supply differing fluids.

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5. The apparatus of claim 1 wherein the zone is adapted to receive fluid effluent from a reactor in the array.

5 6. A process for detecting a chemical reaction producing a sought chemical compound in an array of zones each consisting of or comprising a reactor and containing diverse materials comprising:

10 a. passing electromagnetic radiation into one or more of said zones said electromagnetic radiation having a wavelength absorbed by the sought chemical compound, said radiation passing through the reaction product of said reactor contained in the zone.

15 b. reflecting the electromagnetic radiation which has passed through the reaction product in the zone to pass once again through the reaction product, and

20 c. determining the intensity of the electromagnetic radiation reflected through the material in the zone to determine the presence of the sought chemical compound by the occurrence of absorption of the radiation having the wavelength absorbed by the sought
25 chemical compound.

7. The process of claim 6 wherein the electromagnetic radiation is infrared radiation.

30 8. The process of claim 7 wherein differing fluids are provided to reactors in the array.

9. The process of claim 7 wherein the electromagnetic radiation is generated by a laser.

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10. The process of claim 9 wherein the irradiation is rastered over a plurality of zones of reactors in the array.

5 11. The process of claim 10 wherein the reflected radiation is detected in a form that can generate a video image.

10 12. The process of claim 6 wherein the electromagnetic radiation is monochromatic and is such that only the sought chemical compound will absorb the radiation.

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FOI/0599/29508

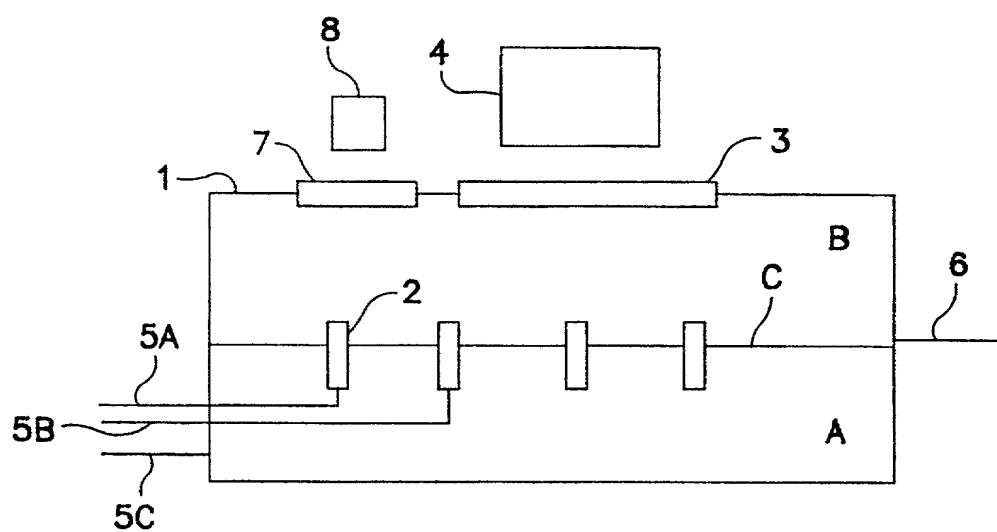


FIG. 1

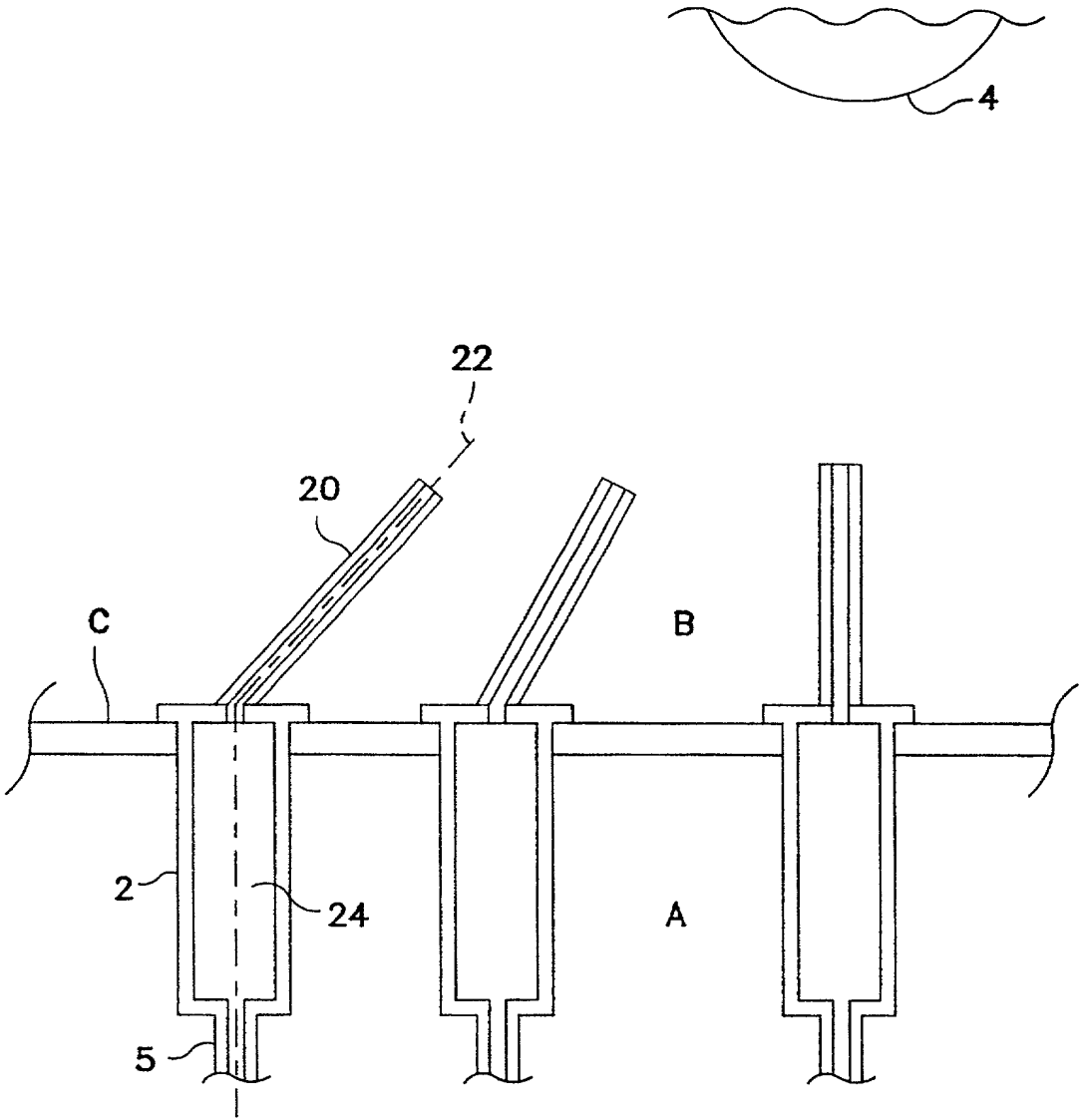


FIG. 2

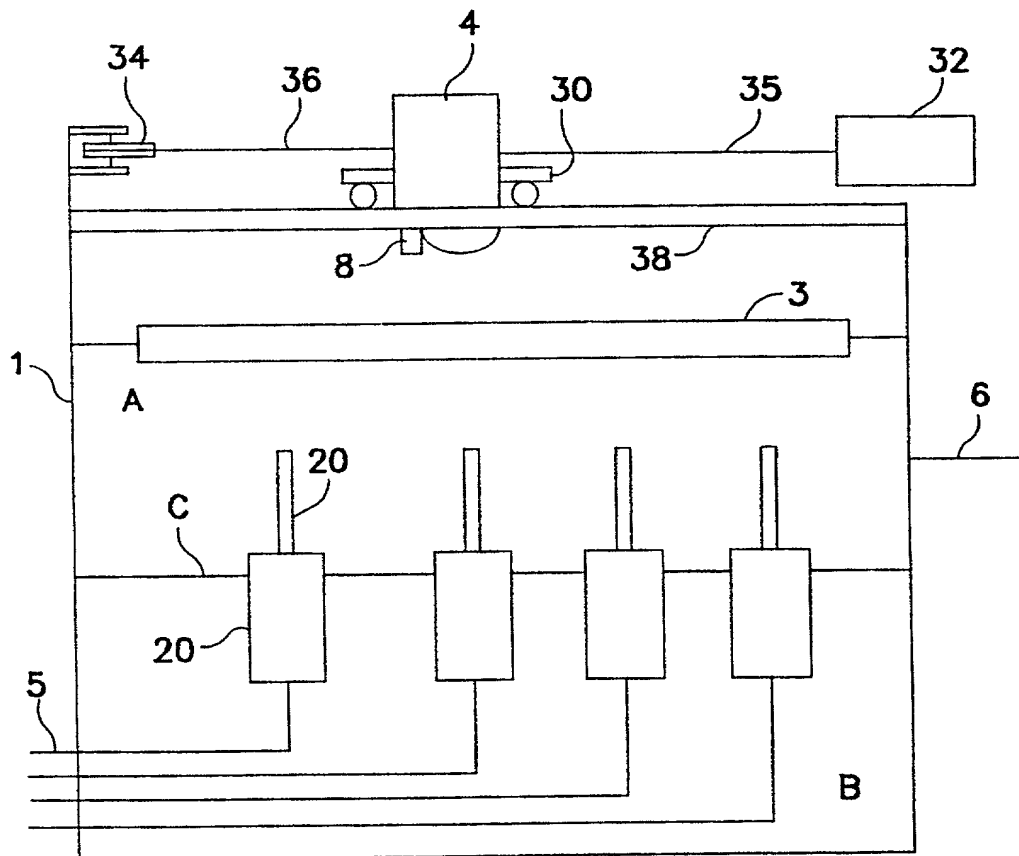


FIG. 3

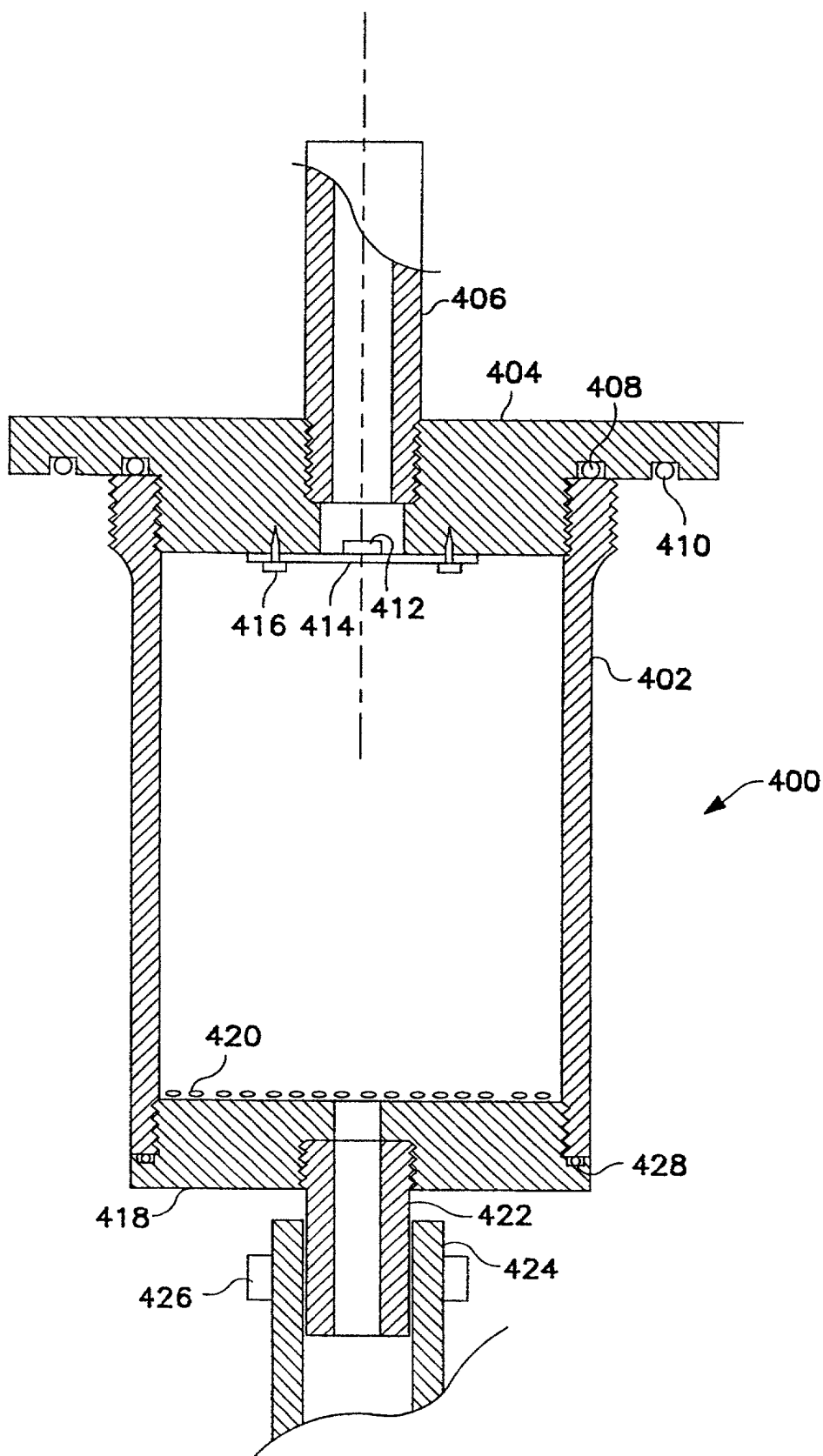


FIG. 4
SUBSTITUTE SHEET (RULE 26)

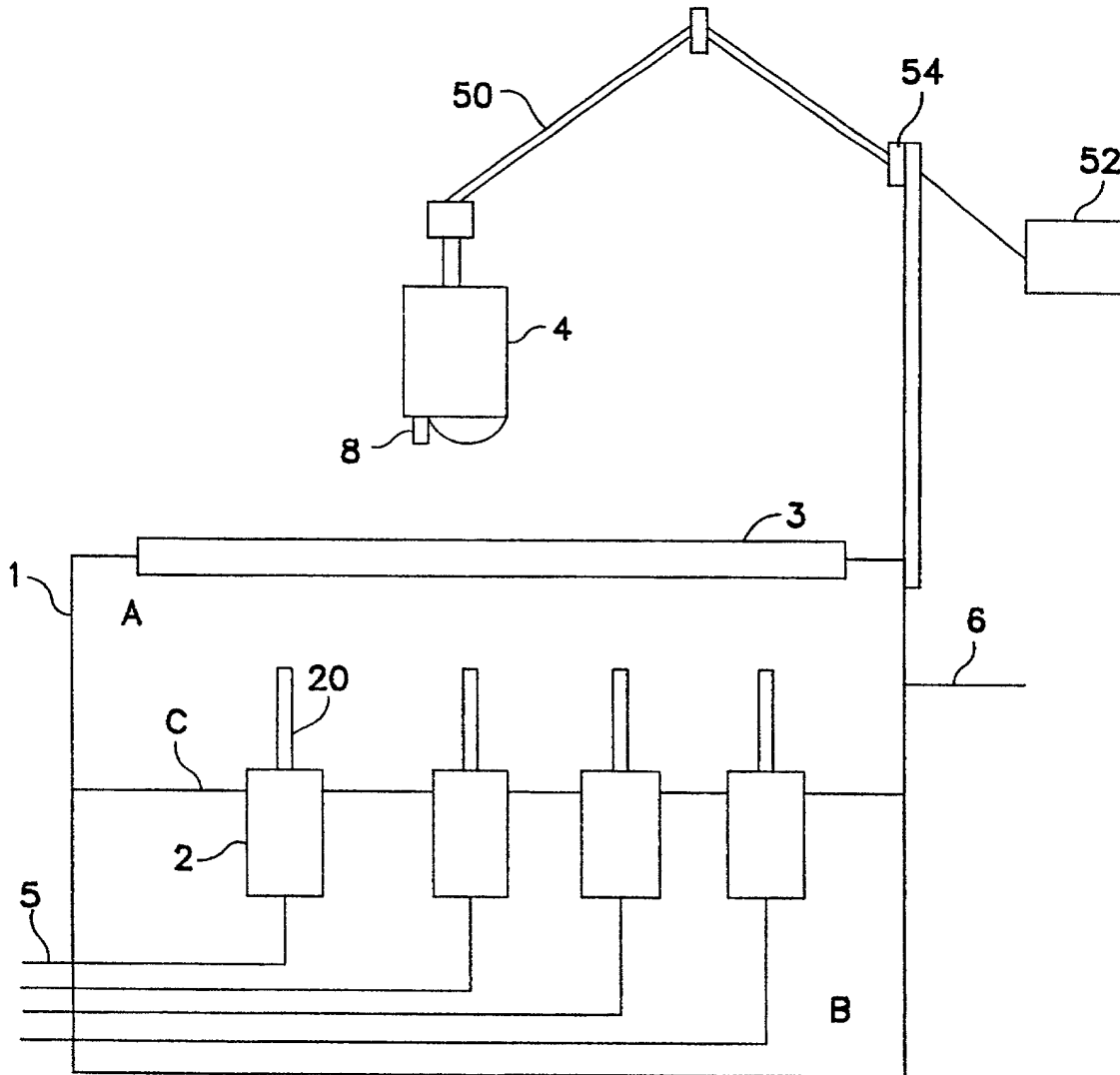


FIG. 5

DECLARATION AND POWER OF ATTORNEY

USA/PCT

As a below named inventor, I hereby declare that:

- (a) My residence and Citizenship are as stated below my name. My P.O. (mailing) address is the same as my residence unless otherwise stated.
- (b) I verily believe I am/we are the original, first and sole/joint inventor(s) of the subject matter that is embraced by and for which a patent is sought on the invention entitled: **APPARATUS AND METHOD FOR COMBINATORIAL CHEMICAL ANALYSIS** and the specification of which: ☐ is attached hereto (____).
(check one) ☒ was filed on December 14, 1999 as (17932).
Application No. PCT/US99/29508
and was amended on _____

- (c) I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
- (d) I acknowledge my duty under 37 CFR 1.56 to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in 37 CFR 1.56(b). If this application is a continuation-in-part application, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 CFR 1.56(b) that became available between the filing date of the prior application from which priority is claimed in part (f) below, and the national or PCT international filing date of this application.
- (e) I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate listed below or § 365(a) of any PCT international application that designated at least one country other than the United States of America listed below, and also identify below any other foreign equivalent application for patent or inventor's certificate or any other equivalent PCT international application having a filing date before that of the application on which priority is claimed:

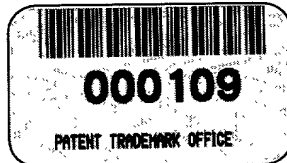
Number	PRIOR FOREIGN APPLICATION(S) Country or PCT	Day/Month/Year Filed	PRIORITY CLAIMED	CERTIFIED COPIES INCL.
<input type="checkbox"/>	Additional claims for benefit are attached.		<input type="checkbox"/>	<input type="checkbox"/>

- (f) I hereby Claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below, or under 35 U.S.C. § 120 of any United States application(s), or under § 365(c) of any PCT international application designating the United States of America listed below:

US or PCT Appln. Serial No.	Filing Date	Status at Application Filing Date
<u>PCT/US99/29508</u>	<u>December 14, 1999</u>	<u>Pending</u>
<u>60/112,360</u>	<u>December 15, 1998</u>	<u>Pending</u>

☐ Additional claims for benefit are attached.

I hereby appoint the attorney(s) and/or agent(s) at the following Customer No. to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith. Address all correspondence to The Dow Chemical Company's appointed counsel at



This appointment, including the right to delegate this appointment, shall also apply to the same extent it is applicable under the laws of the United States of America to any proceedings established by the Patent Cooperation Treaty.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor(s):

At: South Charleston, West Virginia 25309 United States of America
this 4 day of September, 2001

Signature: Louis D'Esposito

Full Name: Louis D'Esposito

Residence: 30 Pope Way

Country: South Charleston, West Virginia 25309 WV

Citizenship: United States of America

P. O. Address: United States of America

Same as Residence

At: _____

this _____ day of _____, 20____

Signature: _____

Full Name: _____

Residence: _____

Country: _____

Citizenship: _____

P. O. Address: _____

At: _____
this _____ day of _____, 20____

Signature: _____

Full Name: _____

Residence: _____

Country: _____

Citizenship: _____

P. O. Address: _____

At: _____

this _____ day of _____, 20____

Signature: _____

Full Name: _____

Residence: _____

Country: _____

Citizenship: _____

P. O. Address: _____

☐ Additional names and signatures are attached.